Carbohydrates

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# Short and Sweet: D-Glucose to L-Glucose and L-Glucuronic Acid**

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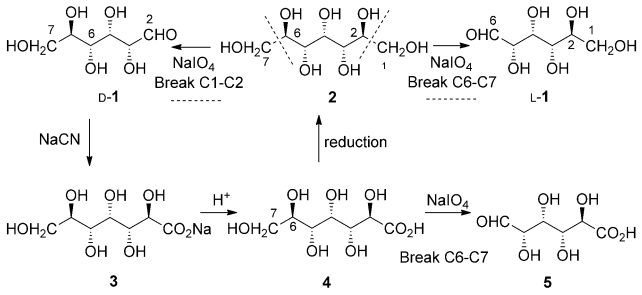
***Abstract:*** *The scarcity and expense of access to* L*-sugars and other rare sugars have prevented the exploitation of their biological potential; for example* D*-psicose, only recently available, has been recognized as an important new food. Here we give the definitive and cheap synthesis of 99.4% pure* L*-glucose from* D*-glucose which requires purification of neither intermediates nor final product other than extraction into and removal of solvents; a simple crystallization will raise the purity to* $>99.8\%$.

L-Sugars are important, usually expensive, and difficult to access.[1] This paper describes the conversion of D-glucose (D-**1**) to L-glucose (L-**1**) in 99.4% purity and to the lactone of L-glucuronic acid **5** by a short scalable sequence that requires neither chromatography nor crystallization of intermediates. On an industrial scale for making chelating agents, D-glucose (D-**1**) undergoes a diastereoselective Felkin–Anh Kiliani ascension with sodium cyanide to give the hydrated sodium salt **3** of D-*glycero*-D-*gulo*-heptonic acid (**4**)[2] at a price of roughly $5000 per metric ton[3] (Scheme 1); D-*gulo* is the Fischer equivalent of L-*gluco*. Periodate cleavage of the C6–C7 diol in **4** leads to L-glucuronic acid (**5**). Reduction of the acid **4** forms the *meso*-heptitol **2**. Regiospecific periodate oxidation of the C6–C7 diol in a protected derivative of **2** forms L-glucose (L-**1**) whereas similar cleavage of the C1–C2 diol leads to D-glucose (D-**1**).




D-**1** **2** L-**1**

**3** **4** **5**

***Scheme 1.*** Conversion of D-glucose (D-**1**) to L-glucose (L-**1**) and L-glucuronic acid **5**.

A single protection step with 2,2-dimethoxypropane (DMP) gave the new triacetonide **6** of methyl glucoheptanoate (Scheme 2), with no trace of the alternative triacetonides **7** or **8** being formed. The hydrolysis of intermediate new diacetonides of glucose **9** and glucuronic acid **10** in the final deprotection is the only step that involves water.

The novel triacetonide **6** was formed by treatment of the hydrated salt **3** with dimethoxypropane (DMP) in the presence of methanolic HCl at reflux for 1 h. Although **6** was the major product, several more polar products were indicated by thin-layer chromatography (TLC). Removal of the solvent followed by extraction of the residue with cyclohexane gave pure triacetonide **6**; no significant further purification was achieved by chromatography. The reaction of 100 g of the salt **3** gave 71 g of the triacetonide **6** (54% yield). The procedure was carried out in a 1 L flask using a magnetic stirrer bead. Although the residue from the reaction could be recycled to provide further **6**, the price of **3** made this a non-cost-effective procedure on this scale. The $^1$H NMR spectrum of the crude cyclohexane extract showed no difference to that of a sample of **6** purified by chromatography (see the Supporting Information).

Two other possible triacetonides, **7** and **8**, might have been formed; both contain six-membered acetonide rings. The $^{13}$C chemical shifts of the three quaternary carbons of the isopropylidene protecting groups at $\delta = 109.8$–$110.7$ are definitively diagnostic of five- (rather than six-) membered acetonides.[4] All acetonides in this paper have a quaternary carbon signal between $\delta = 109.7$–$112.1$.

Selective removal of a terminal acetonide in the presence of other isopropylidene groups by partial acid hydrolysis is usually a reliable procedure. The triacetonide **6** with sulfuric acid in methanol gave an initially clean reaction to afford the diacetonide **11** (Scheme 2); when other products started to appear by TLC, the reaction mixture was quenched by addition of triethylamine. Removal of the solvent gave a mixture consisting of the tri- and diacetonides (**6** and **11**, respectively); 48% of the starting material **6** was recovered by extraction with cyclohexane whereas subsequent extraction with ethyl acetate gave the pure diol **11** in 45% yield (86% yield based on recovered starting material). The $^1$H NMR spectra of the crude extracts of **6** (in cyclohexane) and of the diol **11** (in ethyl acetate) showed no difference to those of samples purified by chromatography (see the Supporting Information).

The diol **11** was the only solid intermediate in the entire sequence. Reduction of the methyl ester **11** with lithium aluminum hydride in THF gave the triol **12** in 93% yield. The diacetonide triol **12** was subjected to the Shing protocol[5] for

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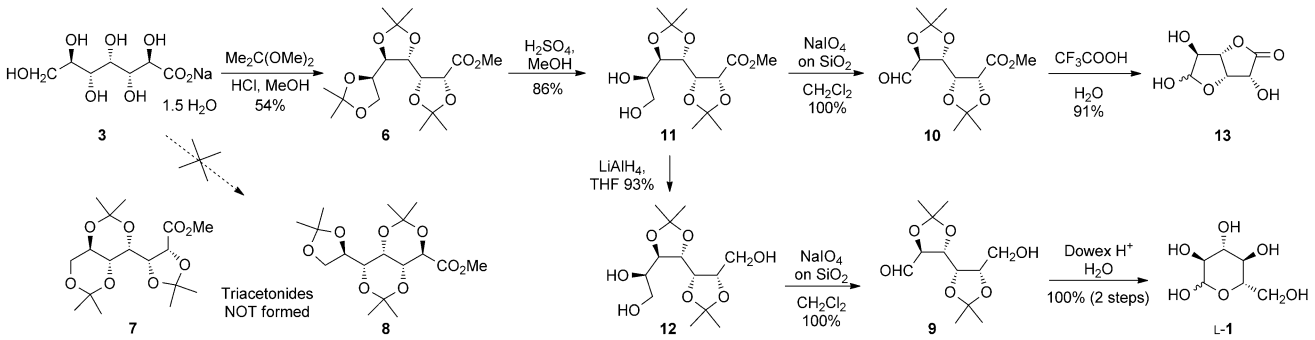


***Scheme 2.*** Synthesis of L-glucose (L-**1**) and L-glucuronolactone **13**.

cleavage of diols by silica-gel-supported periodate in dichloromethane to form the new diacetonide of L-glucose **9** in 100% yield; in general Shing reactions are rapid and quantitative. The corresponding diacetonide of D-glucose D-**9** is unknown. Intermediate **9** without any purification was treated with Dowex $H^+$ in water to give L-glucose (L-**1**) in quantitative yield over the two steps (43% from the salt **3**; 80% from the triacetonide **6**). The $^1H$ NMR spectrum of the crude L-glucose after removal of water was identical (save in the anomer ratio) to that of a sample of L-**1** from a commercial source (see the Supporting Information).

For the synthesis of L-glucuronic acid (**5**), Shing oxidation of the diol ester **11** with periodate gave the new diacetonide of methyl glucuronate **10** in quantitative yield. Intermediate **10** is a stable aldehyde whose NMR spectrum does not change over several days in solution in chloroform; this stable intermediate is likely to be of value as a synthetic intermediate, although its enantiomer D-**10** has not been reported. Removal of the protecting groups from **10** by aqueous trifluoroacetic acid gave L-glucuronolactone **13** in 91% yield from **11** (42% from the salt **3**; 78% from the triacetonide **6**).

The crude L-glucose (L-**1**) so produced was shown by high performance liquid chromatography (HPLC) to be 99.4% pure; for comparison, the purity of samples from two commercial suppliers was found by HPLC to be 99.8% for both samples (the three HPLC traces of these samples L-**1** are shown in the Supporting Information). Thus, the present synthesis of L-**1** requires no purification of any intermediates or the final product by any technique other than extraction into—and removal of—solvents.

Once rare sugars are readily available in sufficient quantity, they are often found to possess a number of unexpected bioactivities. For example D-psicose, produced on a multikilogram scale by the epimerization of C3 of D-fructose,[6] with zero calorific value, is likely to be a widely used food.[7] L-Glucose, almost as sweet as D-glucose, is also not metabolized and has no calorific value.[8] Unlike D-psicose which is absorbed, L-glucose is not a low-calorie food substitute since it has limited oral and intestinal absorption with consequential induction of osmotic diarrhea;[9] the laxative properties make L-**1** a suitable agent for colonoscopy preparation.[10] Ready access to L-glucose will enable a broader study of its potential bioactivities.

Classically, L-glucose has been made by Kiliani ascension of L-arabinose to L-gluconic acid, requiring separation from its C2 epimer; in the subsequent reduction by borohydride care is required to avoid over-reduction and elimination of borate complexes.[11] The simple inversion of configuration at all four chiral carbon atoms in D-gluconic acid to give L-gluconic acid has only appeared in a preliminary report with no indication of yield.[12] Other approaches to L-glucose include those from D-gulonolactone,[13] ab initio asymmetric syntheses,[14] and enzymatic[15] procedures—none of which provide substantial amounts of L-glucose cheaply. The biotechnology of Izumoring[16] has improved the availability of many rare sugars, but the formation of L-glucose is not easy.[17] In 1969 Sowa[18] recognized the value of D-glucoheptonic acid to access L-sugars but the method was not readily scalable; an improvement to the synthesis through benzylidene protection of glucoheptonolactone requires the purification of several intermediates.[19] In contrast this present simple procedure provides easy access to multigram quantities of L-glucose and L-glucuronolactone for use as free sugars or as chirons for complex targets; L-glucose will be of value in the industrial biotechnological preparation of other L-sugars. We also report the synthesis of new acetonides of common sugars in which C1 and C6 of the sugars are unprotected.

## Experimental Section

Preparation of L-glucose (L-**1**): A methanolic solution of hydrogen chloride [prepared by dropwise addition of acetyl chloride (30.0 mL, 430.1 mmol) to methanol (200 mL) under argon at 0 °C] was added to a suspension of sodium α-D-glucoheptonate hydrate **3** ($H_2O$ content 1.5 mol mol$^{-1}$) (100.0 g, 363.6 mmol) in 2,2-dimethoxypropane (500 mL). The reaction mixture was refluxed for 1 h after which TLC (cyclohexane/ethyl acetate, 1:1) showed the formation of a major product ($R_f = 0.66$). Sodium carbonate (160 g) was added to neutralize (the color of reaction mixture turned from brown to light yellow), the solids were removed by filtration, and the solvent was removed in vacuo to give a residue which was extracted with cyclohexane (500 mL). The cyclohexane solution was washed with distilled water (3 × 500 mL) and dried ($MgSO_4$) and the solvent was removed in vacuo to yield the pure triacetonide **6** (71.0 g, 54%).

Without any other purification of **6**, aqueous sulfuric acid (1%, 300 mL) was added dropwise to a stirred solution of **6** (71.0 g, 197.0 mmol) in methanol (700 mL) over a period of 15 min. The reaction mixture was stirred at RT for 4 h after which it was neutralized with triethylamine. Methanol was removed in vacuo and

  

the aqueous residue was extracted with cyclohexane (3 × 150 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo to recover the starting material **6** (34.3 g, 95.2 mmol, 48 %). The aqueous layer was subsequently extracted with ethyl acetate (6 × 150 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo to give **11** as a white solid (28.1 g, 87.7 mmol, 45 %, based on recovered starting material 86 %). Lithium aluminum hydride solution (1M in THF, 123 mL, 122.8 mmol) was added dropwise to a stirred solution of **11** (28.1 g, 87.8 mmol) in THF (130 mL) at −40 °C. The reaction mixture was refluxed for 30 min after which TLC analysis (ethyl acetate) showed no remaining starting material ($R_f = 0.58$) and formation of a single product ($R_f = 0.17$). The excess hydride was quenched by dropwise addition of $NH_4Cl$ (35 mL, sat. aq.) at 0 °C and the resulting mixture was dried ($MgSO_4$), filtered (eluting with ethyl acetate), and concentrated in vacuo to give the triol **12** (23.9 g, 93 %).

Silica-gel-supported $NaIO_4$ (164 g) was added portionwise to a vigorously stirred solution of **12** (23.9 g, 81.8 mmol) in $CH_2Cl_2$ (400 mL). After 30 min, TLC analysis (ethyl acetate) showed no remaining starting material ($R_f = 0.17$) and formation of a single product ($R_f = 0.74$). The mixture was dried ($MgSO_4$) and filtered and the silica gel was thoroughly washed with $CH_2Cl_2$ (4 × 200 mL). The solvents were removed in vacuo to afford the aldehyde **9** (21.4 g, 100 %). The crude aldehyde was dissolved in water (180 mL) and Dowex 50WX8-$H^+$ (≈ 12 g, prewashed with water) was added. After 24 h, TLC analysis (ethyl acetate) showed no remaining starting material and formation of a single product (baseline). The resin was filtered off and washed with water. Removal of water in vacuo afforded pure L-glucose (L-**1**) (14.8 g, 100 % from **12**, 43 % from **3**) as a syrup which slowly formed a white solid, $[\alpha]_D^{20} = -43.6$ ($c = 1.8$, water) compared to commercial sample A $[\alpha]_D^{20} = -47.1$ ($c = 2.1$, water), commercial sample B $[\alpha]_D^{20} = -47.2$ ($c = 2.1$, water) [Lit.[19] $[\alpha]_D^{23} = -52.0$ ($c = 0.80$, water)]. The $^1$H NMR spectrum was identical to that of a commercial sample **11**, other than in the ratio of anomers formed.

Full details of the stepwise procedures and characterization of intermediates is given in the Supporting Information.

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